ARIC Manuscript Proposal #3031

PC Reviewed: 08/08/2017 **Status: _____** **Priority: 2**
SC Reviewed: _____ **Status: _____** **Priority: ____**

1.a. Full Title: Heart Rate Variability Correlation with Psychosocial States and Stressors: the Atherosclerosis Risk In Communities study

b. Abbreviated Title (Length 26 characters): HRV and Emotional States

2. Writing Group:

Writing group members: Amit Shah, MD, MSCR, Anish Shah, MD, Eric Whitsel, PhD, Alvaro Alonso, MD, PhD, Viola Vaccarino, MD, PhD, Elsayed Soliman, MD, MS, MSc

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. ___AS_ **[please confirm with your initials electronically or in writing]**

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3. Timeline: July 2017 – manuscript proposal review
August-September 2017 – analyze data, write paper
October 2017-December 2017– submit paper for peer-review in journal

4. Rationale: The heart and brain are intimately linked through autonomic and other neural networks that facilitate bidirectional communication between the brain and heart.[1,2] A number of studies support the link between autonomic inflexibility, using lower heart rate variability as a

surrogate marker, and major pathophysiologic manifestations (including all-cause mortality, major cardiac events, chronic kidney disease, etc).[3,4] Our research in the Emory Twin Study and other studies revealed an association between decreased heart rate variability and mental health conditions (depression and PTSD).[5] We propose that other psychological states, represented by data from the Social Support Scale, the Spielberger Anger Trait questionnaire, and the Maastricht Vital Exhaustion questionnaire, may be associated with short-term heart rate variability, associate with heart rate variability changes over time, and may help to understand physiologic mechanism related to those emotional states/traits.

1. Thayer JF, Lane RD. A model of neurovisceral integration in emotion regulation and dysregulation. *Journal of Affective Disorders*. 2000;61(3):201-216. doi:10.1016/S0165-0327(00)00338-4.

2. Friedman BH. An autonomic flexibility–neurovisceral integration model of anxiety and cardiac vagal tone. *Biological Psychology*. 2007;74(2):185-199. doi:10.1016/j.biopsycho.2005.08.009.

3. Dekker JM, Crow RS, Folsom AR, et al. Low heart rate variability in a 2-minute rhythm strip predicts risk of coronary heart disease and mortality from several causes. *Circulation*. 2000;102(11):1239–1244.

4. Brotman DJ, Bash LD, Qayyum R, et al. Heart rate variability predicts ESRD and CKD-related hospitalization. *Journal of the American Society of Nephrology*. 2010:ASN–2009111112.

5. Shah A, Vaccarino V. Heart rate variability in the prediction of risk for posttraumatic stress disorder. *JAMA psychiatry*. 2015;72(10):964–965.

5. Main Hypothesis/Study Questions: Our study goal is to examine the relationship of anger, vital exhaustion, and social support (V2, V4) with 2-minute high frequency heart rate variability (V1, V4) over a longitudinal time course. We expect that a decrease in heart rate variability will correlate with increased anger, increased exhaustion, and decreased social support. In addition, we expect that an improvement over the course of follow-up in these psychological states will result in increased heart rate variability.

6. Design and analysis (study design, inclusion/exclusion, outcome and other variables of interest with specific reference to the time of their collection, summary of data analysis, and any anticipated methodologic limitations or challenges if present).

This study is designed as a retrospective cohort study as part of the Atherosclerosis Risk in Communities study. We expect to use data points from multiple visits to examine the relationship between heart rate variability (HRV) and psychosocial data, with the opportunity to examine this relationship over time.

The cohort will include all participants with HRV data in the ARIC database. Exclusion criteria include incomplete data, arrhythmia (atrial fibrillation/flutter, >20% ectopic beats), pacemaker use, sick sinus syndrome, CHD, heart failure, and/or stroke at V1-V4, and loss to follow up or death by visit 4. The primary outcome will be HF HRV, with secondary outcomes including the SDNN, RMSSD, and pNN50. The major exposures include the Interpersonal Support Evaluation List, the Lubben Social Network Scale, the Maastricht Exhaustion Questionnaire, and the Spielberger Trait Anger Scale. These data were collected at Visit 2 and Visit 4.

For outcome, the heart rhythm data has been collected in the form of HRV during visit 1 (2 minutes) and visit 4 (6 minutes) only. The values during visit 1 will be carried over to visit 2, when the psychosocial measures were obtained. Because methods of HRV measurement are different between visits, we will perform a previously published transformation to convert 6 minute HRV metrics of SDNN and RMSSD to their likely 2 minute values (Schoeder *et al., Hypertension* 2003; 43: 1106-1111). However, since no conversion exists for HF HRV, we will also create a normal distribution of HF HRV for both 2-minute and 6 minute measures from a subgroup of healthy subjects aged 55-64 in both V1 and V4, and report the Z score as an indirect measure of HF HRV as it relates to health. Based on the between- and within-visit variances in Schroeder, et al. (2004), the HRV measurements are repeatable over multiple visits. These estimates suggest that as designed, the study is adequately powered.

We will use mixed models to evaluate the relationship between psychosocial states at each visit (main independent variable) and HRV at each visit (main dependent variable). The models will evaluate the longitudinal relationships between baseline psychosocial status and change in HRV over time. The cross-sectional relationships during V1 and V4 will also be assessed. The models will include multivariable adjustment for demographics, medical/CHD risk factors, and cardiac/psychiatric medication use. Subgroup analyses will be done to evaluate for interaction by age, sex, race, antidepressant use, and use of rate controlling agents such as beta-blockers. Methodological limitations include variation in HRV methods from visit 2 to visit 4, temporal difference between HRV testing and emotional testing, potential unmeasured confounders and moderators, and sample heterogeneity.

Abbreviations:
NN: beat-to-beat intervals
SDNN: standard deviation of NN
RMSDD: the room mean successive differences between NN
pNN50: proportion of successive NN that differ by more than 50

7.a. Will the data be used for non-CVD analysis in this manuscript? ____ Yes _X_ No

b. If Yes, is the author aware that the file ICTDER03 must be used to exclude persons with a value RES_OTH = "CVD Research" for non-DNA analysis, and for DNA analysis RES_DNA = "CVD Research" would be used? ____ Yes ____ No
(This file ICTDER has been distributed to ARIC PIs, and contains the responses to consent updates related to stored sample use for research.)

8.a. Will the DNA data be used in this manuscript? ____ Yes __X__ No

8.b. If yes, is the author aware that either DNA data distributed by the Coordinating Center must be used, or the file ICTDER03 must be used to exclude those with value RES_DNA = "No use/storage DNA"? ____ Yes ____ No

9. The lead author of this manuscript proposal has reviewed the list of existing ARIC Study manuscript proposals and has found no overlap between this proposal and previously approved manuscript proposals either published or still in active status. ARIC Investigators have access to the publications lists under the Study Members Area of the web site at: http://www.cscc.unc.edu/ARIC/search.php

__X__ Yes _____ No

10. What are the most related manuscript proposals in ARIC (authors are encouraged to contact lead authors of these proposals for comments on the new proposal or collaboration)?

Brotman DJ, Bash LD, Qayyum R, Crews D, Whitsel EA, Astor BC, Coresh J. 2010. Heart rate variability predicts ESRD and CKD-related hospitalization.. J Am Soc Nephrol. 21(9):1560-70.

Schroeder EB, Chambless LE, Liao D, Prineas RJ, Evans GW, Rosamond WD, Heiss G. 2005. Diabetes, glucose, insulin, and heart rate variability: the Atherosclerosis Risk in Communities (ARIC) study.. Diabetes Care. 28(3):668-74.

Schroeder EB, Whitsel EA, Evans GW, Prineas RJ, Chambless LE, Heiss G. 2004. Repeatability of heart rate variability measures.. J Electrocardiol. 37(3):163-72.

Schroeder EB, Liao D, Chambless LE, Prineas RJ, Evans GW, Heiss G. 2003. Hypertension, blood pressure, and heart rate variability: the Atherosclerosis Risk in Communities (ARIC) study.. Hypertension. 42(6):1106-11.

Liao D, Carnethon M, Evans GW, Cascio WE, Heiss G. 2002. Lower heart rate variability is associated with the development of coronary heart disease in individuals with diabetes: the atherosclerosis risk in communities (ARIC) study.. Diabetes. 51(12):3524-31.

Dekker JM, Crow RS, Folsom AR, Hannan PJ, Liao D, Swenne CA, Schouten EG. 2000. Low heart rate variability in a 2-minute rhythm strip predicts risk of coronary heart disease and mortality from several causes: the ARIC Study. Atherosclerosis Risk In Communities..Circulation. 102(11):1239-44.

Liao D, Sloan RP, Cascio WE, Folsom AR, Liese AD, Evans GW, Cai J, Sharrett AR. 1998. Multiple metabolic syndrome is associated with lower heart rate variability. The Atherosclerosis Risk in Communities Study.. Diabetes Care. 21(12):2116-22.

Liao D, Evans GW, Chambless LE, Barnes RW, Sorlie P, Simpson RJ, Heiss G. 1996. Population-based study of heart rate variability and prevalent myocardial infarction. The Atherosclerosis Risk in Communities Study.. J Electrocardiol. 29(3):189-98.

Liao D, Barnes RW, Chambless LE, Heiss G. 1996. A computer algorithm to impute interrupted heart rate data for the spectral analysis of heart rate variability--the ARIC study.. Comput Biomed Res. 29(2):140-51.

Liao D, Barnes RW, Chambless LE, Simpson RJ, Sorlie P, Heiss G. 1995. Age, race, and sex differences in autonomic cardiac function measured by spectral analysis of heart rate variability--the ARIC study. Atherosclerosis Risk in Communities.. Am J Cardiol. 76(12):906-12.

11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? ____ Yes _X_ No

11.b. If yes, is the proposal

___ A. primarily the result of an ancillary study (list number* _____)

___ B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables; list number(s)* _____ _____ _____)

*ancillary studies are listed by number at http://www.cscc.unc.edu/aric/forms/

12a. Manuscript preparation is expected to be completed in one to three years. If a manuscript is not submitted for ARIC review at the end of the 3-years from the date of the approval, the manuscript proposal will expire.

12b. The NIH instituted a Public Access Policy in April, 2008 which ensures that the public has access to the published results of NIH funded research. It is **your responsibility to upload manuscripts to PubMed Central** whenever the journal does not and be in compliance with this policy. Four files about the public access policy from http://publicaccess.nih.gov/ are posted in http://www.cscc.unc.edu/aric/index.php, under Publications, Policies & Forms. http://publicaccess.nih.gov/submit_process_journals.htm shows you which journals automatically upload articles to PubMed central.

13. Per Data Use Agreement Addendum, approved manuscripts using CMS data shall be submitted by the Coordinating Center to CMS for informational purposes prior to publication. Approved manuscripts should be sent to Pingping Wu at CC, at pingping_wu@unc.edu. I will be using CMS data in my manuscript ____ Yes _X__ No.